REMARKS

Claim 1 has been amended to specify that the C-terminal anchoring domain mediates anchoring, support for which can be found on page 7 lines 23-27 of the Specification. The recitation that the recombinant polypeptides of claim 1 are bivalent or multivalent has been moved into new dependent claim 41.

In claim 2, the limitation that the linker molecule comprises a plurality of hydrophilic amino acids has been moved to dependent claim 42.

In claim 4, the recitation that a transfected filamentous phage produces an embodiment of the display system of the present invention has been deleted.

Claims 4, 6, 8, 12-13, 16, 20-26, 27-28, 33 and 35 have been grammatically amended.

Claim 9 has been amended to recite the N-terminal blocking domain is the N2 domain of filamentous phage gene product III. Support for this amendment can be found in the Specification on page 7 lines 15-27.

The duplication of the limitation, "bi or multivalent," has been deleted from claim 11.

Optional limitations formerly recited in claims 12, 28 and 29 have been moved into new dependent claims 38, 39 and 40, respectively.

Claims 14 and 15 have been amended to depend from claim 40.

The limitation deleted from claim 19 regarding the hydrophilic nature of a particular linker of the invention is recited in dependent claim 37.

Claim 21 has been amended into independent format; it recites limitations previously recited in claim 1.

Claims 22-24, 30-32 and 34-35 have been amended to specify that the polypeptides and nucleotides of the invention are isolated.

Claims 22, 30 and 34 have been amended to specify that the claimed epitope binding domain is comprised of at least 3 CDRs. Support for this amendment can be found in the Specification, page 6 lines 4-7.

The claims have been amended to more clearly describe the current invention, and no new matter has been introduced.

1. Interview Summary

Applicants thank the Examiner for courtesies extended in the Interview on August 24, 2006. Discussions focused on the indefiniteness and enablement rejections of the April 24, 2006 Office Action.

2. Objections to the Specification

The Examiner has objected to the Specification for containing embedded hyperlinks. Applicants respectfully traverse.

Applicants have deleted all embedded hyperlinks, thereby obviating the rejection.

The Examiner has objected to claims 21 and 27 as allegedly improper multiple dependent claims depending from multiple dependent claims. Applicants respectfully traverse.

Applicants have amended claim 21 into independent form, thereby obviating the rejection. Applicants also point out that claim 27 depends from claims 23 or 24 in the alternative, claim 23 depends only from claim 1 and claim 24 is an independent clam. So the objection to claim 27 is improper.

3. Rejections Under 35 USC § 112¶1 – Enablement

The Examiner has rejected claims 22-35 as allegedly not enabled. The Examiner observers that Applicants recite the epitope binding domains of the invention comprise at least one CDR of the scFv fragment according to any one of SEQ ID Nos. 61, 63, 65, 67, 69, 71, 73, 75 and 77. The Examiner then states Applicants disclose that six (6) CDRs of a V_H-V_L dimer collectively confer antigen binding specificity to an antibody, and urges it is well established that all six CDRs must be in their proper order and location for a V_H-V_L dimer to have epitope binding function. The Examiner concludes that reciting an epitope binding domain comprises one CDR causes enablement problems for the present invention (Office Action pages 3-4). Applicants respectfully traverse.

As a preliminary matter, Applicants point out that they have amended the claims to specify the epitope binding domains of the invention comprise at least 3 CDRs. At a substantive level, Applicants call the Examiner's attention to the fact that it is also well known and disclosed by Applicants that:

> "*Even a single variable domain (or half of an Fv comprising only three CDRs specific for an epitope) has the ability to recognize and bind epitope, although at a lower affinity than an entire binding site*" (Painter (1972) Biochem. 11:1327-1337) (Specification, page 6 lines 4-7).

Because it is both well known and disclosed by Applicants that a variable region of three (3) CDRs has the ability to recognize and bind epitope, a person of ordinary skill in the art, based on his/her own knowledge and Applicants' disclosure, would be able to practice the claimed invention without undue experimentation.

In further support of the enablement of the present invention, Applicants have submitted the declaration of Dr. Tobias Raum. In his declaration, Dr. Raum confirms that the molecular techniques required to construct the synthetic epitope binding domains of the invention in which CDRs are operably linked by peptide linkers (Specification page 2, lines 13-16 and page 13, lines 18-24) were well known in the art at the time the present application was filed. Dr. Raum

provides U.S. Pat. #5,225,539 as further evidence of the state of the art at the time the present application was filed. (U.S. Pat. #5,225,539, Raum Declaration).

Dr. Raum also establishes that he, as one of ordinary skill in the art, knows how to identify the precise amino acid sequences of CDRs within variable heavy and light chain sequences, and provides a seminal reference which provides the foundation of that knowledge (Kabat et al. *Sequences of Proteins of Immnological Interest*, Fifth Edition (1991), Raum Declaration).

In addition, Dr. Raum identifies the amino acid sequences of the CDRs within the V_H and V_L chains of the present invention: SEQ ID NOs: 61, 63, 65, 67, 69, 71, 73, 75 and 77 (Table, Raum declaration).

The Examiner also states that even minor changes in the amino acid sequences of variable regions may dramatically affect their epitope binding function, which causes enablement problems (Office Action, page 4 lines 5-7). Applicants submit this statement does not apply to the present invention.

It is well known that, in nature, epitope binding domains are located at the extreme N-terminus of an antibody, and epitope binding domains identified by traditional methods typically lose their binding function when positioned C-terminally of amino acid sequences or protein domains: *e.g.* in the context of a recombinant polypeptide (Specification, page 3 lines 1-9). It is a novel and non-obvious object of the present invention to provide a method for identifying epitope binding domains which maintain their specific binding function when located C-terminally of amino acid sequences or protein domains in recombinant polypeptides.

One embodiment of the present invention achieves this objective by screening libraries of epitope binding domains, comprised of variable regions, for the ability to bind a predetermined epitope when N-terminally blocked (Specification, page 1, lines 1-5, 1st¶). Specifically, binding variable regions identified in this manner are then moved, intact, from the screening vector of the invention into a C-terminal position in a recombinant polypeptide of the invention, where they maintain their specific binding function. So, the present invention does not involve changing the

amino acid sequence of variable regions; but rather involves moving intact variable regions of the invention into the recombinant proteins and polypeptides of the invention.

It follows that the Examiner's statement regarding the effects of changing amino acid sequences of variable regions is irrelevant to the present invention, and is not a valid basis upon which to impose an enablement rejection.

Based on the foregoing, Applicants submit the present invention is fully enabled.

3. Rejections Under 35 USC §112¶2 - Indefiniteness

The Examiner has rejected claims 1-36 under 35 USC §112¶2 as allegedly indefinite. The Examiner states it is not clear what the "N-terminal blocking domain" in claim 1 is, and to what "blocking" Applicants refer. The Examiner also states it is not clear that, in claim 9, the C-terminal domain should be the N-terminal domain (Office Action, page 5). Applicants respectfully traverse.

With respect to the "N-terminal blocking domain," Applicants call the Examiner's attention to the disclosure found on page 7 lines 5-27 of the Specification. There, Applicants define an "N-terminal blocking domain" as a stretch of amino acids or a protein domain located N-terminally of an epitope binding domain in the screening vectors of the present invention.

With respect to the "blocking" to which Applicants refer, it is well known that epitope binding domains of natural antibodies are at the extreme end of the N-terminus: that is they are C-terminal of zero (0) amino acids. It is also well known, and disclosed by Applicants, that epitope binding domains identified by traditional methods typically lose their specific binding function when placed C-terminal of a stretch of amino acids, unlike those identified by the method of the present invention (Specification, page 3 lines 1-13). It follows that Applicants' "N-terminal blocking domain" blocks an epitope binding domain's specific recognition of a target epitope when such recognition is dependent on the epitope binding domain being located at the extreme N-terminus of a protein.

Based on the foregoing discussion, Applicants submit they have clearly defined the "N-terminal blocking domains" of the invention as well as the "blocking" it performs.

Turning to the Examiner's rejection of claim 9, Applicants have amended the claim to recite the N2 domain of filamentous phage gene III is the N-terminal blocking domain, thereby obviating the rejection.

For the foregoing reasons, Applicants submit that the indefiniteness rejections are without basis, and should be withdrawn.

In view of the above amendments and remarks, Applicants respectfully request reconsideration of the rejections and allowance of the claims.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), the Applicant respectfully petitions for a three (3) month extension of time for filing a response in connection with the present application and the required small entity fee of $510.00 is to be charged to Deposit Account No. 02-2448.

If the Examiner has any questions concerning this application, the Examiner is requested to contact the undersigned at (714) 708-8555 in our Southern California office.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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